REMARKS

Reconsideration of the rejection of all claims is respectfully requested in view of the following amendments and arguments. Claims 1-12 were initially filed with this application, and are noted as pending in the Office Action Summary.

Claim Amendments

Claims 1 and 2, directed toward the production of a vascular damaging effect in a warm-blooded animal, have been cancelled in order to expedite prosecution of this application to allowance and to focus the claims more directly on the "treatment of a cancer involving a solid tumour" as claimed in claims 3 and 4, and as demonstrated in the examples and other evidence discussed below.

Claims 3 and 4 have been amended as a formality to remove the phrase "such as a human." Such recitations of a species or sub-species within the scope of a broader genus ("warm-blooded animal") recited in that same claim are generally not allowed under U.S. practice. The deletion of this phrase is being made out of recognition of this principle, and the deletion of "such as a human" is not intended to reduce the scope of this claim inasmuch as administration to a "human" is already encompassed within the genus "warm blooded animal."

Claims 7-12 have been canceled as being in a "use" format not generally accepted under U.S. practice. The substance of claims 7-12 is believed to already be claimed in claims 1-6. Therefore, this amendment is not intended to in any way reduce the scope of the invention being claimed.

The above amendments are being made without abandonment or prejudice to Applicants' right to prosecute any deleted subject matter in one or more continuing applications. Following entry of these amendments, claims 3-6 remain pending in this application.

Claim Rejections -- 35 U.S.C. §103

Claims 1-12 have been rejected under 35 U.S.C. 103(a) as being obvious over WO 01/74368 Al ("hereinafter Davis *et al.* ") in view of Harari, P., *et al.*, *Radiation Response*

Modification Following Molecular Inhibition of Epidermal Growth Factor Receptor Signaling, Seminars in Radiation Oncology, vol. 11, no. 4, October 2001, pages 281-289 (hereinafter "Harari *et al.*").

Davis *et al.* is said to teach a method for the production of vascular damaging effect and a method for the treatment of cancer in a warm-blooded animal which comprises the administration of an effective amount of ZD6126 or a pharmaceutically acceptable salt thereof in a combination therapy before, after or simultaneously with an effective amount of a taxane, ionizing radiation or a platinum anti-tumor agent.

Harari *et al.* is said to teach ZD1839 as being well-known in the art as an anti-tumor agent for many cancers[1] as a small molecule tyrosine kinase inhibitor (citing page 282, col. 1, lines 29-41) that when combined with chemotherapy or selected chemotherapy agents has the capacity to enhance the cytotoxicity of radiation across a spectrum of human cancer cell lines (Page 283, col. 2, lines 16-26, page 284, and page 285, col. 1, lines 1-4).

From this the Examiner asserts that one of ordinary skill in the art would be motivated to combine the teachings of Davis *et al.* with the teachings of Harari *et al.* "because the references teach overlapping subject matter, most notably, the treatment of cancer and cancer treatment-related conditions with chemotherapeutic and anti-cancer agents." The Examiner further asserts that,

> In light of the foregoing, one of ordinary skill in the art would be motivated to apply the teachings of Harari *et al.* and Davis *et al* to the present invention, because ZD1839 is anti-tumor agent that when combined with other anti-cancer agents and/or ionizing radiation, effectively treats cancerous tumors through EGFR signal modulation and ZD6126 is known to produce vascular damaging effects and to treat cancer involving solid tumors. When used together, it would be obvious to one of ordinary skill in the art that the proliferation of cancers and their associated tumors, would be diminished and vascular damaging effects

[1] The Examiner here cites Miyata, H. *et al.*, *The Effects Of ZD1839 (Iressa), A Highly Selective EGFR Tyrosine Kinase Inhibitor, As A Radiosensitiser In Bile Duct Carcinoma Cell Lines*, International Journal of Oncology, vol. 28, 2006 pages 915-921), without explanation. To the Extent that Miyata is somehow relied upon as supplementing Harari *et al.*, the Examiner is reminded that Miyata, having been published in 2006, is not prior art to the present invention. In any event, Miyata *et al.* does not suggest combination therapy with ZD6126 and ZD1839. Rather, Miyata *et al.* discloses the combination of ZD1839 with radiation in the treatment of bile duct cancer, and there is no suggestion in Miyata *et al.* of using ZD1839 in combination with other anti-cancer agents.

enhanced through the combination therapy of ZD6126 and ZD1839 with ionizing radiation.

(Action at page 3).

This ground for rejection is respectfully traversed.

Present claims 3 and 4 are directed toward the treatment of a cancer involving a solid tumor in a warm-blooded animal. The treatment of claim 3 comprises administering to said animal an effective amount of ZD6126 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of ZD1839 or a pharmaceutically acceptable salt thereof. The treatment of claim 4 comprises administering to said animal an effective amount of ZD6126 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of ZD1839 or a pharmaceutically acceptable salt thereof and before, after or simultaneously with an effective amount of ionizing radiation.

Claim 5 is directed to a pharmaceutical composition and claim 6 is directed to a kit, both comprising ZD6126 or a pharmaceutically acceptable salt thereof and ZD1839 or a pharmaceutically acceptable salt thereof.

It is respectfully submitted that there is no teaching or suggestion in the prior art of a combination therapy of ZD6126 and ZD1839 for the treatment of any cancer, whether or not also in combination with ionizing radiation. There also is no teaching or suggestion in the prior art of a pharmaceutical composition or kit that combines ZD6126 and ZD1839 as presently claimed.

The Examiner correctly points out that Davis *et al.* discloses the use of ZD6126 together with, specifically, a taxane, a platinum anti-tumor agent or ionizing radiation. However, there is no suggestion in Davis *et al.* of using ZD6126 with the compound ZD1839 (also known as Iressa or gefitinib).

The Examiner also points to the disclosure of Harari *et al.* as disclosing that ZD1839, which "when combined with chemotherapy or selected chemotherapy agents has the capacity to enhance the cytotoxicity of radiation across a spectrum of human cancer cell lines," citing page 283, col. 2, line 16 through page 285, col. 1, line 4.

More specifically, as one would surmise from its title (*Radiation Response Modification Following Molecular Inhibition of Epidermal Growth Factor Receptor*

Signaling) Harari *et al.* is focused on the combination of certain epidermal growth factor receptor (EGFR) inhibitors (including ZD1839) in combination with radiation therapy, and does not itself disclose the combination of ZD1839 with any other identified chemotherapeutic agent. Apparently the Examiner is referring to the general characterization other literature references that are cited as background in Harari *et al.* Thus, Harari *et al.* notes at page 283, col. 2:

> Preclinical studies show clear activity of ZD1839 in human tumor cells with potentiation of cytotoxity with selected chemotherapy agents.[23] Similarly, preliminary studies confirm the capacity of ZD1839 to enhance the cytotoxity of radiation across a spectrum of human cancer cell lines including those from lung, pancreas, and head and neck.[24,25]"

(Emphasis added). Harari *et al.* continues at page 284, col. 2 through page 285, col. 1, line 4:

> Although the clinical trials to date have focused on ZD1839 alone or in combination with conventional chemotherapy agents,[5] the in vitro data suggests that the favorable interaction of ZD1839 with radiation warrants evaluation of this combination therapy in future clinical studies.

In support of these statements Harari *et al.*, in footnote 23, refers to Ciardiello *et al*: *Antitumor effect and potentiation of cytotoxic drugs activity in human cancer cells by ZD-1839 (Iressa), an epidermal growth factor receptor-selective tyrosine kinase Inhibitor.* Clinical Cancer Research 6:2053-2063, 2000, which reference has already been formally cited in the Information Disclosure Statement submitted with the application. Ciardiello *et al.* disclose pre-clinical data showing that certain conventional cytotoxic drugs such as paclitaxel, docetaxel and oxaliplatin etc. may be combined with ZD1839.[2] However, there is no disclosure or suggestion in Ciardiello *et al.* of combining ZD1839 with the specific compound ZD6126 in accordance with the present invention. Therefore, even if a skilled person were to consider the teaching of Harari *et al.* and the cited Ciardiello *et al.* reference, that person would have been motivated to combine ZD1839 with one of the cytotoxic drugs disclosed in Ciardiello *et al.*, such as paclitaxel or a platinum-derived compound, but in so

[2] The full list of cytotoxic drugs tested in combination with ZD1839 consists of three platinum-derived compounds (cisplatin, carboplatin, and oxaliplatin), two taxanes (paclitaxel and docetaxel), two topoisomerase II inhibitors (doxorubicin and etoposide), a topoisomerase I inhibitor (topotecan) and a thymidylate synthase inhibitor (raltitrexed).

doing the skilled person would not have arrived at the specific combinations of the presently claimed invention.

Similarly, the references of footnotes 5 and 24 in the above-quoted passage from Harari *et al.* do not suggest combining ZD1839 with ZD6126 in accordance with the present invention.

Footnote 5 of Harari *et al.* cites Baselga J: *New technologies in epidermal growth factor receptor-targeted cancer therapy,* Signal 1:12-21, 2000. Baselga notes at page 14, second column that preclinical studies with ZD1839 show that it has an "additive or supra-additive effect when used in combination with other, cytotoxic agents, noting table 2 fig. 3. Table 2 notes studies in which ZD1839 was co-administered with carboplatin, cisplatin, paclitaxel, docetaxel, edatrexate, gemcitabine, topotecan, and ralitrexed, and fig. 3 graphically depicts the antitumor activity of ZD1839 alone and in combination with tomudex. However, there is no disclosure or suggestion of co-administering ZD1839 with ZD6126 in accordance with the present invention, whether or not also with ionizing radiation. This Baselga reference is cited in the Supplemental Information Disclosure Statement submitted herewith and a copy of the reference is provided.

Footnote 24 of Harari *et al.* cites Williams KJ, Telfer BA, Stratford IJ, et al: *Combination of ZD1839 (Iressa"), and EGFR-TKI, and radiotherapy increases antitumour efficacy in a human colon cancer xenograft model,* Proc Am Assoc Cancer Res 42, 2001, (abst 3840). Williams *et al.* investigated combination of ZD1839 with single dose and factionated radiotherapy on in a LoVo xenograft model. However, again, there is no disclosure or suggestion of co-administering ZD1839 with ZD6126 in accordance with the present invention. This Williams *et al.* abstract is cited in the Supplemental Information Disclosure Statement submitted herewith and a copy of the abstract is provided.

Footnote 25 of Harari *et al.* cites Raben D, Phistry M, Helfrich B, et al: *ZD1839 (Iressa), a selective epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), enhances radiation (RT)-induced cytotoxicity in human pancreatic and cholangiocarcinoma cell lines in vitro,* Gastrointestinal Cancer Research Conference, Orlando, FL, November, 2000 (hereinafter "Raben *et al.* (2000)"). Neither Applicant nor the undersigned have been able to locate or obtain a copy of Raben *et al.* (2000), but from the title it would appear to

also be focusing on ZD1839 enhancing radiation-induced cytotoxicity, and rather than the co-administration of ZD1839 and ZD6126 in accordance with the present invention. It would be very much appreciated if the Examiner could search the databases available to her at the U.S. Patent and Trademark Office for a copy of this article to complete the record with respect to the Harari *et al.* reference that has been cited and applied by the Examiner.

Therefore, it is respectfully submitted that there is no teaching or suggestion in Davis *et al.* and Harari *et al.*, even if considered together and/or with the additional documents discussed above, that would motivate the skilled person to treat a cancer involving a solid tumor with the combined therapy of ZD1839 and ZD6126 as presently claimed, nor to combine ZD1839 and ZD6126 in a pharmaceutical composition or kit.

The Examiner appears to be asserting that it would be *prima facie* obvious to combine ZD6126 with ZD1839 in light of Davis *et al.* and Harari *et al.* simply because both documents relate to the treatment of cancer, and/or that Davis *et al.* and Harari *et al.* each *separately* teach that ZD6126 and ZD1839, respectively, enhance the cytotoxicity of ionizing radiation. It is respectfully submitted, however, that when the *specific* teachings of these references are read *in their entirety* and the prior art considered *as a whole* by the *skilled* person, that such an assertion would be seen as an impermissible over generalization of the teachings of these two references.

It is a well established, but often overlooked, principle that when considering and applying a prior art reference to a rejection, the prior art reference must be considered as a whole. This point is made in the MPEP in setting out the guidelines for ascertaining the differences between the prior art and the claimed invention, where it is stated that:

> A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L.Gore & Associates, Inc. v. Garlock, Inc.* 721 F.2d 1540 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

(MPEP § 2141.02 at page 2100-124; emphasis in original).[3]

The Examiner must consider the relevant art as a whole, also taking into account circumstances present at the time of the invention which taught away from Applicant's

[3] All references to the MPEP are to the 8th Edition, Revision 5, August 2006.

solution. In upholding the validity of the patent in issue, the Federal Circuit noted in *Akzo N.V. v. United States Int'l Trade Comm'n*, 808 F.2d 1471, 1481, 1 USPQ2d 1241, 1246 (Fed. Cir. 1986):

> As the ALJ recognized, prior art references before the tribunal must be read as a whole and consideration must be given where the references diverge and teach away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock , 721 F.2d 1540, 1550, 220 USPQ 303, 311 (Fed. Cir. 1983), cert. denied , 469 U.S. 851 (1984). Moreover, appellants cannot pick and choose among individual parts of assorted prior art references "as a mosaic to recreate a facsimile of the claimed invention."

(721 F.2d at 1552, 220 USPQ at 312; emphasis added). See also, *Panduit Corp. v. Dennison Manufacturing Co.*, 810 F.2d 1561, 1568 (Fed. Cir. 1987).

As discussed above, when the references and the art are considered as a whole, it is submitted that the teachings of Davis *et al.* and Harari *et al.* (and references cited therein) might direct the skilled person to combinations of ZD1839 with radiation, or with the various conventional chemotheraputic agents mentioned, but they do not provide any motivation to the skilled person to specifically select ZD1839 and combine it with the specific compound ZD6126 in a therapeutic treatment, pharmaceutical composition or kit as presently claimed. Therefore, it is respectfully submitted that *prima facie* obviousness of the present claims has not been established, and this ground for rejection should be withdrawn.

Nevertheless, *even if* a person skilled in this art were somehow motivated to combine ZD6126 and ZD1839 in a method of treating a solid tumor cancer, it is respectfully submitted that there is nothing in the prior art that would suggest that such a treatment would have any particularly beneficial effect.

In this regard, the Examiner's attention is drawn to the examples of the present application, in particular to the results in the LoVo tumor model described in paragraphs [0076] to [0082] of the subject application (published as US 2005/0215530). As discussed in paragraph [0082] the combination of ZD6126 and ZD1839 significantly delayed tumor growth compared to the use of either ZD6126 alone or ZD1839 alone. Furthermore, the delay in tumor growth was greater than the sum of the growth delay produced by both agents alone

(see last sentence of paragraph [0082]). The greater-than-additive effect of combining ZD6126 and ZD1839 could not have been predicted based upon the teaching in the cited prior art.

This greater-than-additive effect resulting from the combined therapy of ZD6126 and ZD1839 is *confirmed* by the following three later-published documents:

Raben *et al*, Mol. Cancer Therapeutics, 2004, 3(8), 977 – 983 (hereinafter "Raben *et al.* (2004)");

Guy *et al*, AACR November 2003; and

Bozec *et al*, British Journal of Cancer (2006), 1-7.

It is understood that each of the above-three papers resulted from research sponsored by Applicant's assignee, AstraZeneca, and the authors of the Guy *et al.* poster (including AJ Ryan, the inventor on the present application) were employed by or otherwise associated with AstraZeneca at the time of its preparation.

Raben *et al.* (2004), Bozec *et al.* and Guy *et al.* are cited in (and copies are provided with) the Supplemental Information Disclosure Statement being filed herewith. The relevant disclosure of each of these references is noted below.

Raben *et al.* (2004)

The study reported in Raben *et al.* (2004) was undertaken to evaluate novel strategies with ZD6126 in the treatment of NSCLC [non-small cell lung cancer] and to evaluate its effects with radiation or ZD1839. The results indicate, *inter alia*, that the combination of ZD6126 and ZD1839 produced significantly greater tumor growth inhibition compared to either agent alone (see p. 980, col. 1, paragraph 1 and Table 1). Moreover, the results of the triple combination of radiation therapy, ZD6126 and ZD1839 on the growth of established A549 xenografts resulted in a still further tumor growth inhibition compared to each treatment alone or in double combinations.

Guy *et al.* (2003)

Guy *et al.* make the observation that the use of ZD6126 in the LoVo tumor xenograft model results in necrosis of the central portions of a tumor, leaving a viable rim of tumor tissue. Guy *et al.* show that this remaining rim of tumor tissue exhibits phospho-EGFR (pEGFR) in the viable rim of the tumor (see bullets 2 and 3 in the conclusions). Accordingly

the inhibition of EGFR tyrosine kinase using ZD1839, may indicate why the particular combination of ZD6126 and ZD1839 according to the invention provides such surprising beneficial effects, in the sense that the ZD1839 will target the EGFR tyrosine kinase in the remaining viable rim of tumor tissue, thereby producing an enhanced anti-tumor effect. Bozec *et al.* (2006)

The surprising effect resulting from the presently claimed combination of ZD6126 and ZD1839 is confirmed in Bozec *et al.* For example in the CAL33 model, it was found that the use of ZD6126 alone at the doses studied provided no significant anti-tumor effects. However, when combined with ZD1839, the combination showed a super-additive effect on tumor growth relative to either agent alone (see Fig 5A and page 6, col. 1).

Nothing in the art cited by the Examiner or discussed above would lead a skilled person to use in combination therapy the *vascular damaging agent* ZD6126 and the EFGR tyrosine kinase inhibitor ZD1839, no less to expect that such a combination therapy would have the particularly beneficial results noted in the specification and confirmed by Raben *et al.* (2004), Guy *et al.* and Bozec *et al.*, as discussed above.

It is therefore respectfully submitted that *prima facie* obviousness has not been established, but *even if* it were, any *prima facie* obviousness is overcome by the unexpected more-than-additive benefits demonstrated in the specification, and confirmed by the later published studies of Raben *et al.* (2004), Guy *et al.* and Bozec *et al.* Accordingly, withdrawal of the obviousness rejection and allowance of all claims are believed to be in order, and are respectfully requested.

Supplemental Information Disclosure Statement

The Examiner's attention is respectfully directed toward the Supplemental Information Disclosure Statement being submitted simultaneously herewith citing and providing a copy of the additional documents discussed above. Consideration of these documents is respectfully requested, together with an acknowledgement of such consideration by returning an initialed copy of the form PTO-1449 to the undersigned.

Conclusion

It is believed that all grounds for rejection have been addressed and overcome by the above amendments and the foregoing remarks, supported by the specification disclosure of unexpected results achieved by the claimed combination as confirmed by the Raben *et al.* (2004), Guy *et al.* and Bozec *et al.* Withdrawal of all grounds for rejection and the allowance of all claims are believed to be in order, and are respectfully requested. However, if any issues remain, it is respectfully suggested that the Examiner telephone the undersigned in order to expedite the resolution thereof.

Except for issue fees payable under 37 C.F.R. §1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. §1.136(a)(3).

Respectfully Submitted,
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Date: September 24, 2007 By: _____

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